REMARKS

In view of the above amendments and the following remarks, reconsideration of the outstanding office action is respectfully requested.

The rejection of claims 2-25 under 35 U.S.C. § 112 (1st para.) for lack of enablement is respectfully traversed.

It is the position of the U.S. Patent and Trademark Office ("PTO") that the claimed invention is enabled only for a rodent model of pemphigus vulgaris using immune cells from a donor deficient in auto-antigen Dsg3. The PTO has based this position on the assertion that the practice of the invention requires knowledge of the detailed phenotype of the knockout (i.e., donor) animal. Moreover, the PTO is concerned with the availability of such an animal.

First of all, contrary to the assertion of the PTO, one need not know the "detailed knockout phenotype" of the donor animal to practice the claimed invention. Rather, one need only know two things:

(a) that the animal is deficient in the target gene of interest (i.e., "lacks a gene encoding an antigen protein of an autoimmune disease"), a finding that can be made using routine and conventional techniques (e.g., detection of the absence of target mRNA using RT-PCR; detection of the absence of target protein using Western blot; detection of transcription of a selected reporter gene, such as a radioactive or fluorescent marker gene; etc.); and

(b) that immune cells are produced.

Thus, applicants respectfully submit that the availability of a suitably characterized donor animal commensurate with the practice of the claimed invention is well within the purview of one skilled in the art without undue experimentation, from the disclosure of the patent coupled with information known in the art.

The PTO cites Pearson, H., "Surviving a Knockout Blow," *Nature* 415:5-9 (2002) ("Pearson"), in support of its position. Pearson says "indeed, clear and consistent phenotypes now seem to be the exception rather than the rule." However, in contrast to the suggestion of the PTO, this article seems to support the enablement of the instant invention. For example, Pearson says that "[i]n many cases, a mutant mouse does not show any obvious characteristics - or phenotype" (see page 8, lines 12-14 from the bottom of the left column). Pearson further says that "[m]any mouse genes belong to families whose functions overlap and this 'redundancy' may mean that a clear phenotype only emerges when two or more genes are removed," (see page 9, lines 22-26 of the left column). These arguments suggest

that most knockout mice will show no particular phenotype, i.e., look normal. Thus, from this context, the sentence cited by the PTO should actually read that "clear and consistent *abnormal* phenotypes seem to be the exception rather than the rule." Thus, as taught by Pearson, one skilled in the art would understand that a discernible "mutant" phenotype is not expected when dealing with knockouts. It follows then, that one skilled in the art would not expect or require a detailed phenotype of the knockout in order to practice the claimed invention using a knockout donor meeting the limitations of claim 2 (i.e., a donor that "(a) lacks a gene encoding an antigen protein of an autoimmune disease and (b) develops immune cells, and wherein the recipient (i) is the same species as the donor, (ii) has the same genetic background and/or is immunodeficient, and (iii) following the transplantation, produces an antibody reactive to the antigen protein and/or has activated T cells reactive to the antigen protein") or claim 3 (i.e., a donor that "(a) lacks a gene encoding an antigen protein of an autoimmune disease; (b) develops immune cells and (c) has been immunized with the antigen protein, and wherein the recipient (i) is the same species as the donor, (ii) has the same genetic background and/or is immunodeficient, and (iii) following the transplantation, produces an antibody reactive to the antigen protein and/or has activated T cells reactive to the antigen protein") of the present invention.

Although the PTO states that "[t]he skilled artisan could not practice the invention without first carrying out undue experimentation to make a homozygous knockout" (see Final Office Action, page 5, lines 4-6), applicants respectfully submit that in light of the minimal requirements on the claimed donor animal, as discussed above, one skilled in the art could readily make and use the present invention from the disclosure of the present application.

On the issue of availability of suitable donor animals, the PTO cites to several articles disclosing transgenic animals. For example, Logan et al., "Potential Use of Genetically Modified Pigs as Organ Donors for Transplantation Into Humans," *Clin. Exp. Pharmacol. Physiol.* 26:1020-25 (1999) "(Logan") is cited, which says that "the challenge in the development of transgenics is not in this process, but in the design of the construct that will allow for the *expression of the gene of interest in the desired cell type at an appropriate level*" and "*problems with obtaining expression of transgenes in animals* have been related to the inability to routinely obtain high levels of expression, especially over multiple generation, and the observation of variegated expression, whereby not all cells in an organ will express the gene" (emphasis added). However, it should be noted that the problem of *protein expression* is limited to transgenic animals and is not relevant to knockout animals, as the

basis for knockouts is *gene deletion* rather than *gene expression*. Applicants respectfully submit that the removal of a gene is a much more straightforward and routine process than the functional insertion of a transgene.

In addition, applicants submit that the preparation of knockout animals has reached a level of high predictability, as is evidenced, for example, by the availability of specific vectors designed for the preparation of knock-outs, and the rise of commercial enterprises that offer preparation of knock-out animals on an as-needed basis (see e.g., the web pages of inGenious Targeting Laboratory, Inc.; genOway; and Genomatix, Ltd., offering knock-out vectors and knock-out mice and rat provider services, attached hereto as Exhibits 1-3, respectively). Thus, applicants submit that one of ordinary skill in the art would be fully able to identify and obtain a knockout animal suitable for use within the context of the instantly claimed invention without undue experimentation.

The Selection of the Autoantigen

Regarding the lack of enablement rejection of claims 2-25, the PTO notes that the instant specification "fails to teach any other antigen knockout animal besides Dsg3-/-" (Final Office Action, page 3). Furthermore, the concern is raised that, given the current state of the art of autoimmunity, autoantigens responsible for a particular disease are either not clearly defined or not limited to one protein (see Final Office Action, page 3, lines 2-4 from the bottom). However, the fact that the donor immune cells may be used to create antibodies against only one (or a few) of a plurality of autoantigens associated with a particular autoimmune disease does not undermine the operability or utility of the recipient animal as a model of that particular autoimmune disease.

Furthermore, applicants respectfully submit that the disclosed working example is sufficiently illustrative such that other autoimmune/autoantigen combinations would be readily apparent to one skilled in the art and, therefore, that other such embodiments are within the scope of enablement. For example, contrary to the PTO's suggestion, many autoimmune diseases were well characterized at the time of invention. Indeed, at the time of invention, numerous autoantigens had been positively identified. Examples of specific autoimmune disease/autoantigen combinations known in the art are described in Table 1, below. In the previous response, it was argued that the knockout mice of TSH receptor gene, which encodes an autoantigen of Grave's disease, are viable. In addition, knockouts of the genes described in Table 1 have been also shown to be viable.

TABLE 1

Autoimmune Disease	Autoantigen	Autoantigen Reference	Knockout Reference
Autoimmune Polyglandular Syndrome Type 1	P450 1A2	Clement et al., *J Clin. Endocrinol. & Metabol.* 82:1353-1361 (1997)	Liang et al., *Proc. Natl Acad. Sci. USA* 93:1671-1676 (1996)
Halothane Hepatitis	P450 2E1	Eliasson et al., *Mol. Pharmacol.* 50:573-582 (1996)	Lee et al., *J. Biol. Chem.* 271:12063-12067 (1996).
Autoimmune Polyendocrine Syndrome	Tryptophan hydroxylase	Ekwall et al., *Lancet* 352:279-283 (1998)	Walther et al., *Science*, 299:76 (2003)
Celiac Disease	Tissue trans-glutaminase 2	Dieterich et al., *Nat. Med.* 3:797-801 (1997)	Laurenzi et al., *Mol. Cell. Biol.* 21:148-155 (2001)
Systemic Lupus Erythematosus	Ro	McCauliffe et al., *J. Invest. Dermatol.* 100:73S-79S (1993)	Xue et al., *Proc. Natl. Acad. Sci. USA* 100:7503-7508 (2003)
Insulin-dependent Diabetes Mellitus	Islet cell auto-antigen 69 (ICA69)	Pietropaolo et al., *J. Clin. Invest.* 92:359-371 (1993)	Winer et al., *J. Immunol.* 168:475-482 (2002)
Insulin-dependent Diabetes Mellitus	IA-2	Lan et al., *Proc. Natl. Acad. Sci. USA* 93:6367-6370 (1996)	Saeki et al., *Diabetes* 51:1842-1850 (2002)
Insulin-dependent Diabetes Mellitus	GAD65	Kaufman et al., *J. Clin. Invest.* 89:283-292 (1992)	Asada et al., *Biochem. Biophys. Res. Commun.* 229:891-895(1996)
IgA Pemphigus	Desmocollin 1	Hashimoto et al., *J. Invest. Dermatol.* 109:127-131 (1997)	Chidgey et al., *J. Cell Biol.* 155:821-832 (2001)
Stiff-Man Syndrome	Amphiphysin 1	De Camilli et al., *J. Exp. Med.* 178:2219-2223 (1993)	Di Paolo et al., *Neuron* 33:789-804 (2002)
Rasmussen's Encephalitis	GluR3	Rogers et al., *Science* 265:648-651 (1994)	Meng et al., *Neuron* 39:163-176 (2003)

Copies of all references listed in Table 1 for autoantigens are attached hereto as Exhibit 4, and copies of all references listed in Table 1 for the corresponding knockouts are attached hereto as Exhibit 5.

As evidenced by Table 1, a multitude of autoimmune diseases have been characterized at the genetic level. Furthermore, a viable gene-deficient animal model for each of these genes has been disclosed. This list, while not exhaustive, is indicative of the state of the art in autoimmune disease identification, as well as that of knockout technology. Thus, applicants submit that the disclosure of the present invention, taken with the knowledge

of a skilled scientist regarding the identification and characterization of numerous autoimmune diseases and the responsible autoimmune/autoantigen combinations, the availability of corresponding knockout animals, and the highly developed state of the art with respect to making knockout animals, provides one of ordinary skill in the art with sufficient guidance to produce additional embodiments of the claimed invention.

Therefore, a skilled scientist, having read the present application would have been fully able to practice the claimed invention.

Predicting the Effect of the Knockout

Another concern raised by the PTO relates to the effect of the knockout on the viability of the resulting phenotype. The PTO states that "it is unpredictable whether a correlating autoimmune disease phenotype could be reproduced upon transplantation of the immune cells from the knockout." See Final Office Action, page 4, lines 5-7. Regarding the former, it is clear that the claimed invention is not applicable to the study of all autoimmune diseases and/or all autoantigens. Indeed, as the PTO suggests, some knockout donor animals may not be viable. However, it is well accepted that the presence of inoperative embodiments within the scope of a claim does not necessarily render that claim non-enabled. *See Atlas Powder Co. v. El. du Pont de Nemours & Co.*, 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984); MPEP 2164.08(b). In the instant case, one skilled in the art would readily recognize that the "antigen of an autoimmune disease" cannot constitute an essential protein if the knockout animal is to be viable. Thus, applicants respectfully submit that one skilled in the art could distinguish between operative and inoperative embodiments with only minimal effort.

Furthermore, the technique of "adoptive transfer," in which immune cells from a donor of interest are transplanted to a host in which the immune responsiveness has been eliminated, is a well-known method used for the study of immune cells and of the cellular interactions required in an immune response. See Kuby, J., *Immunology* Chap. 2, pg. 24 Freeman and Company, New York (1992) (attached hereto as Exhibit 6). The literature is replete with reports in which adoptive transfer has been used to transfer immune cells to a host individual for immunological investigations of disease conditions and for *in vivo* therapeutic treatment. (See e.g., Abstracts of various articles using the adoptive transfer methodology from 1983 to 2001, attached hereto as Exhibit 7). Therefore, one of ordinary skill in the art would have been fully familiar with adoptive transfer techniques and would have a high expectation of success when used in accordance with the claimed invention.

Moreover, as discussed in applicants' previous response, the claimed recipient animal need not exhibit a phenotype corresponding to a particular autoimmune disease. Rather, all that is required by the present claims is that the recipient animal "produces an antibody reactive to the antigen protein and/or having activated T cells reactive to the antigen protein" (see independent claims 2 and 3, for example). Therefore, the display of symptoms or characteristics of a particular autoimmune disease is not an element of the claimed invention. Rather, a striking feature of the present invention is the creation of an animal that produces an antibody against a self-antigen and the use of such an animal in the study of autoimmune conditions. Even in autoimmune diseases that involve multi-antigens, the instant invention remains applicable for producing antibodies against one or a few auto-antigens, thereby inducing an autoimmune response against these antigens in the recipient. Even in this respect autoimmune animal models made according to the present invention would have great utility in investigation of disease states and potential treatments thereof.

Therefore, a skilled scientist, having read the present application, would have known how to make additional "rodent recipient[s] transplanted with immune cells from a rodent donor" in accordance with the present invention, where following transplantation, the recipient "produces an antibody reactive to the antigen protein and/or has activated T cells reactive to the antigen protein."

Accordingly, the rejection of claims 2-25 under 35 U.S.C. § 112 (1st para.) for lack of enablement is improper and should be withdrawn.

In view of all the foregoing, applicants submit that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

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February 6, 2004 — Jo Ann Whalen
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